UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

01/AUG/2008

MEMORANDUM

Subject:	Name of Pesticide Product:	SC 465 Herbicide
	EPA File Symbol:	264-RNAA
	DP Barcode:	D340543
	Decision No.:	379125
	Action Code:	R01.0
	PC Codes:	015804 (thiencarbazone-methyl)
		123000 (isoxaflutole)

From: Eugenia McAndrew, Biologist
Technical Review Branch
Registration Division (7505P)

To: Hope Johnson, RM Team 25
Herbicide Branch
Registration Division (7505P)

Applicant: Bayer CropScience LP
P.O. Box 12014
2 T.W. Alexander Drive
Research Triangle Park, NC 27709

FORMULATION FROM LABEL:

Active Ingredient(s):	% by wt.
Thiencarbazone-methyl	7.6
Isoxaflutole	19.0
Inert Ingredient(s):	73.4
Total:	100.0%

ACTION REQUESTED: RM requests: "Bayer CropScience has submitted a new end-use product that is a combination of the new AI thiencarbazone-methyl and the AI isoxaflutole. The AI thiencarbazone-methyl is currently under tri-lateral review with the UK and PMRA, however this product is not part of the tri-lateral review due to the change in use pattern for isoxaflutole, but is linked to the data. They have submitted acute toxicology data in support of this end-use product. I have included the submission details, labels and csfs along with the studies in this bean."

BACKGROUND: Bayer CropScience LP has submitted a six pack of acute toxicity studies to support the registration of the proposed product, SC 465 Herbicide, EPA File Symbol 264-RNAA. The studies were conducted at Bayer HealthCare AG, PH-PD Toxicology International, 42096 Wuppertal, Germany and Bayer CropScience, France with assigned MRID numbers 471140-15 to -20. A CSF dated January 22, 2007 for a basic formulation is included in the submission. This new active ingredient, thiencarbazone-methyl, is part of a tri-lateral review with Canada, the UK and the US. The UK conducted the primary review of the six studies in OECD format. Canada and the US performed secondary reviews.

RECOMMENDATIONS:

1. The acute oral, acute dermal, acute inhalation, primary eye irritation and primary skin irritation studies have been reviewed and are classified as acceptable.

2. The dermal sensitization study (LLNA; mouse; OECD 429; OPPTS 870.2600) is classified as supplemental. The 2003 OPPTS harmonized guidelines state the "LLNA is the preferred method, where applicable." The "where applicable" correlates to the performance parameters in the appendix - the 1999 ICCVAM report. In 1999, ICCVAM validated the method using 209 "single compound compounds" but did not validate the assay for mixtures. The appendix clearly states the LLNA should not be used for metals, aqueous solutions, and mixtures. In January 2008, ICCVAM updated the validation report on LLNA regarding mixtures, metals and aqueous solutions. ICCVAM findings are that when compared to the guinea pig it has a false negative rate of 50%, a false positive rate of 44%, and accuracy rate of 53% in mixtures. Due to these limitations, TRB questioned whether the negative result found in this study is correct. TRB decided to perform a weight of the evidence approach for this joint review chemical by obtaining information on each component (inert ingredient) in this mixture. After reviewing the components sensitization potential, TRB determined that most were non-sensitizers. Therefore, to avoid further animal testing, TRB will classify the study as "supplemental" and recommend label language as a non-sensitizer.

3. The acute toxicity profile for SC 465 Herbicide, EPA File Symbol 264-RNAA, is as follows:

Acute oral toxicity	III	Acceptable	MRID 47114015
Acute dermal toxicity	III	Acceptable	MRID 47114016
Acute inhalation toxicity	IV	Acceptable	MRID 47114017
Primary eye irritation	III	Acceptable	MRID 47114018
Primary skin irritation	IV	Acceptable	MRID 47114019
Dermal sensitization	Neg.	Supplemental	MRID 47114020

LABELING: Based on the toxicity profile above, the following are the precautionary and first aid statements for the proposed product as obtained from the Label Review System:

PRODUCT ID #: 000264-01066

PRODUCT NAME: SC 465 Herbicide

PRECAUTIONARY STATEMENTS

SIGNAL WORD: CAUTION

Hazards to Humans and Domestic Animals:

Harmful if absorbed through skin. Harmful if swallowed. Causes moderate eye irritation. Avoid contact with skin, eyes or clothing. [Wear protective eyewear.]* Wear long-sleeved shirt and long pants, socks, shoes, and chemical-resistant gloves (such as Natural Rubber, Selection Category A).

*[Protective eyewear may be specified, if appropriate.]

First Aid:

If on skin: Take off contaminated clothing. Rinse skin immediately with plenty of water for 15-20 minutes. Call a poison control center or doctor for treatment advice.

If swallowed: Call a poison control center or doctor immediately for treatment advice. Have person sip a glass of water if able to swallow. Do not induce vomiting unless told to by a poison control center or doctor. Do not give anything to an unconscious person.

If in eyes: Hold eye open and rinse slowly and gently with water for 15-20 minutes. Remove contact lenses, if present, after the first 5 minutes, then continue rinsing. Call a poison control center or doctor for treatment advice.

Have the product container or label with you when calling a poison control center or doctor or going for treatment. You may also contact 1-800-xxx-xxxx for emergency medical treatment information.

User Safety Recommendations:

Wash thoroughly with soap and water after handling and before eating, drinking, chewing gum, or using tobacco. Remove and wash contaminated clothing before reuse.

Reviewer: Pesticides Safety Directorate, UK **Date: August 1, 2008**
Risk Manager (EPA): RM 25

Acute oral toxicity

BYH 18636 + AE 0001789 + IFT SC 465 (also called BYH 18636 + Isoxaflutole + AE 0001789 SC 90 + 225 + 150 g/L or thiencarbazone-methyl + isoxaflutole + AE 0001789 SC 90 + 225 + 150 g/L) is an suspension concentrate formulation (SC) containing BYH 18636 (thiencarbazone-methyl) at 90 g/L, isoxaflutole at 225 g/L and AE 0001789 at 150 g/L

Report:	**KIIIA1 7.1.1/01; Schuengel M., 2006**
Title:	BYH 18636 + Isoxaflutole + AE 0001789 SC 90 + 225 + 150 g/L - Acute toxicity in the rat after oral administration
Citation:	Schungel, M. (2006) BYH 18636 + Isoxaflutole + (Inert Ingredient) SC 90 + 225 150 g/l: Acute Toxicity in the Rat after Oral Administration. Project Number: AT03049, T/7076608, M/273329/01/1. Unpublished study prepared by Bayer Ag Inst. of Toxicology. 29 p. May 23, 2006. MRID No. 47114015
Report No & Document No	AT03049, T7076608 M-273329-01-2
Guidelines:	OECD Guidelines No 423 (2001). EEC Directive 67/548/EEC Annex V, B1.tris (1967) in its current version EPA (OPPTS 870.1100 – 712-C-98-190), August 1998
Deviation(s):	The test compound is a product known to be stable and homogenous in both undiluted and in ready-to-use formulation with water. Therefore, analytical determinations of stability and homogeneity of the aqueous formulations were not performed. The deviation does not limit the assessment of the results.
GLP	Yes

I. Materials and methods

A. Materials

1. Test material:	BYH 18636 (7.26%w/w) + Isoxaflutole (18.3% w/w) + AE 0001789 (12.1% w/w) SC 90 + 225 + 150 g/L
Specification no.:	102000013459
Description:	White milky liquid
Lot/Batch no.:	2005-004304
Content:	BYH 18636: 90 g/L, Isoxaflutole 225 g/L, AE 0001789: 150 g/L (Nominal values) BYH 18636: 85.2 g/L, Isoxaflutole 215 g/L, AE 0001789: 142 g/L (Certified by analysis)
Stability of test compound:	Guaranteed for study duration; expiry date: 16th Dec. 2006

2. Vehicle and/or positive control: Tap water

3. Test animals

Species:	Rat, females
Strain:	Wistar (Hsd CpPb:Wu)
Age:	10-12 weeks approximately
Weight at dosing:	172 g – 194 g
Source:	Harlan/Winkelmann GmbH, Borchen, Germany
Acclimatization period:	At least 5 days
Diet:	Provimi Kliba 3883.0.15; Kaiseraugst, Switzerland
Water:	Tap water *ad libitum*
Housing:	The animals were group caged conventionally in polycarbonate cages on low dust wood granulate bedding (J. Rettenmaier & Söhne, 73479 Ellwangen-Holzmühle, Germany). The cages of the animals were placed on racks. The wood granulate was randomly checked for contaminants at regular intervals and the results have been stored at the Department for Laboratory Animal Services, Bayer HealthCare AG, Wuppertal, Germany. Room temperature: 22 ± 2°C; Air humidity: 55 ± 5%; Ventilation: approx. 10 changes per hour; Light/ Dark cycle : 12 hour rhythm

B. Study design and methods

1. Animal assignment and treatment

Dose:	2000 mg/kg bw
Application route:	Oral by gavage
Application volume:	10 mL/kg bw
Fasting time:	For administration, food was withheld from the animals for approximately 16 - 24 h before administration of the test compound, and they were fed again approximately 2-4 h after administration
Group size:	3 rats/dose group
Post-treatment observation period:	14 days
Observations:	Mortality, clinical signs, body weight, gross necropsy
In life dates:	9th March 2006 to 29th March 2006

The test compound was formulated in tap water; and the test material was administered per os in a single dose (2000 mg/kg) by gavage to 3 fasted female Wistar rats. As no mortality occurred, three additional animals were treated with the same dose.

II. Results and discussion

A. Mortality

Mortality was not observed at 2000 mg/kg bw.

Table 7.1.1-1 Doses, mortality / animals treated

Dose (mg/kg bw)	Toxicological results*			Occurrence of signs	Time of death	Mortality (%)
Females						
2000 1st	0	0	3	--	--	0
2000 2nd	0	0	3	--	--	0
acute oral LD_{50}: > 2000 mg/kg bw						

* 1st number = number of dead animals; 2nd number = number of animals with signs; 3rd number = number of animals used

B. Clinical observations

No clinical signs were observed.

C. Body weight

Body weight and body-weight gain were not affected by the treatment.

D. Necropsy

No particular gross pathological changes were observed in animals sacrificed at the end of the study period.

III. Conclusion

According to EPA guidelines, the LD_{50} for this formulation is greater than 2000 mg/kg, which is consistent with the criteria for EPA Toxicity Category III.

EVALUATION, SUMMARY AND CONCLUSION BY REGULATORY AUTHORITY	
Name of authority	Pesticides Safety Directorate, UK
Reviewer's comments	Reliability rating: totally reliable The study (T7076608) is fully compliant with OECD 423 (2001) No treatment-related findings were observed in this study.
Conclusions	The acute oral LD_{50} of the test material in female rats was found to be >2000 mg/kg bw under the conditions of this study. The product is not classified for acute oral toxicity according to current EC criteria.

Reviewer: Pesticides Safety Directorate, UK **Date: August 1, 2008**
Risk Manager (EPA): RM 25

Acute dermal toxicity

Report:	**KIIIA1 7.1.2/02; Schuengel M., 2006**
Title:	BYH 18636 + Isoxaflutole + AE 0001789 SC 90 + 225 + 150 g/L - Acute toxicity in the rat after dermal administration
Citation:	Schungel, M. (2006) HYN 18636 + Isoxaflutole + (Inert Ingredient) SC 90 + 225 +150 g/l: Acute Toxicity in the Rat After Dermal Application. Project Number: T/8076609, AT03067, M/279655/01/1. Unpublished study prepared by Bayer Ag Inst. of Toxicology. 29 p. May 24, 2006. MRID No. 47114016
Report No & Document No	AT03067, T8076609 M-279655-01-2
Guidelines:	OECD Guidelines N° 402 (1987) EEC Directive 67/548/EEC Annex V, B.3 (1967) EPA (OPPTS 870.1200 – 712-C-98-192, August 1998)
GLP	Yes

I. Materials and methods

A. Materials

1. Test material:	BYH 18636 (7.26%w/w) + Isoxaflutole (18.3% w/w) + AE 0001789 (12.1% w/w) SC 90 + 225 + 150 g/L
Specification no.:	102000013459
Description:	White milky liquid
Lot/Batch no.:	2005-004304
Content:	BYH 18636: 90 g/L, Isoxaflutole 225 g/L, AE 0001789: 150 g/L (Nominal values) BYH 18636: 85.2 g/L, Isoxaflutole 215 g/L, AE 0001789: 142 g/L (Certified by analysis)
Stability of test compound:	Guaranteed for study duration; expiry date: 16th Dec 2006
2. Vehicle and/or positive control:	None
3. Test animals	
Species:	Rat, males and females
Strain:	Wistar (Hsd Cpb:WU)
Age:	9 – 13 weeks approximately
Weight at dosing:	Males: 241 g – 250 g Females: 213 g – 220 g
Source:	Harlan/Winkelmann GmbH, Borchen, Germany

Acclimation period:	At least 5 days
Diet:	Provimi Kliba 3883.0.15; Kaiseraugst, Switzerland
Water:	Tap water *ad libitum*
Housing:	The animals were caged individually in polycarbonate cages on low dust wood granulate bedding (J. Rettenmaier & Söhne, 73479 Ellwangen-Holzmühle, Germany). The cages of the animals were placed on racks. The wood granulate was randomly checked for contaminants at regular intervals and the results have been stored at the Department for Laboratory Animal Services, Bayer HealthCare AG, Wuppertal, Germany. Room temperature: 22 ± 2°C; Air humidity: 55 ± 5%; Ventilation: approx. 10 changes per hour; Light/Dark cycle: 12 hour rhythm.

B. Study design and methods

1. Animal assignment and treatment

One day before the start of the treatment the back and flanks of 5 male and 5 female Wistar rats were shorn. They received a single dermal dose of 2000 mg/kg bw of the pure liquid test compound applied semi-occlusively. After an exposure time of 24 hours, the dressings were removed and the treated area was rinsed with tepid water using soap and gently patting the area dry.

Dose (mg/kg bw)		**Surface area (cm^2)**	**Range of doses (mg/cm^2)**
males	2000	12.0	40.2-41.7
females	2000	12.0	35.5-36.7

Application route:	Dermal, semi-occlusive dressing
Duration:	24 hours
Group size:	5 rats/sex/group
Post-treatment observation period:	14 days
Observations:	Mortality, clinical signs, skin effects, body weight, gross necropsy
In life dates:	9th March 2006 to 23rd March 2006

II. Results and discussion

A. Mortality

Mortality was not observed at 2000 mg/kg bw.

Table 7.1.2-1 Doses, mortality / animals treated

Dose (mg/kg bw)	Toxicological results*			Duration of signs	Time of death	Mortality [%]
Males						
2000	0	0	5	--	--	0
Females						
2000	0	0	5	--	--	0
acute dermal LD_{50}: > 2000 mg/kg bw						

* 1st number = number of dead animals:; 2nd number = number of animals with signs; 3rd number = number of animals in the group

B. Clinical observations

No clinical signs were observed.

C. Body weight

Body weight and body weight gain was not affected by treatment in males or females.

D. Necropsy

No particular gross pathological changes were observed in animals sacrificed at the end of the study period.

III. Conclusion

The dermal LD_{50} of the formulation BYH 18636 + Isoxaflutole + AE 0001789 SC 90 + 225 + 150 g/L is greater than 2000 mg/kg body weight for both male and female rats, which is consistent with the criteria for EPA Tox Category III.

EVALUATION, SUMMARY AND CONCLUSION BY REGULATORY AUTHORITY	
Name of authority	Pesticides Safety Directorate, UK
Reviewer's comments	Reliability rating: totally reliable The study (T8076609) is fully compliant with OECD 402 (1987) Minimal weight loss was seen in one female rat during the first week of the study, however all animals gained weight over the study period. No additional treatment-related findings were observed in this study.
Conclusions	The acute dermal LD_{50} of the test material in female rats was found to be >2000 mg/kg bw under the conditions of this study. The product is not classified for acute dermal toxicity according to current EC criteria.

Reviewer: Pesticides Safety Directorate, UK **Date: August 1, 2008**
Risk Manager (EPA): RM 25

Acute inhalation toxicity to rats

Report:	**KIIIA1 7.1.3/01; Pauluhn J., 2006**
Title:	BYH 18636 + Isoxaflutole + AE 0001789 SC 90 + 225 + 150 g/L - Acute inhalation toxicity in the rat
Citation:	Pauluhn, J. (2006) BYH 18636 + Isoxaflutole + (Inert Ingredient) SC 30 + 225 + 150 G/L: Acute Inhalation Toxicity in Rats. Project Number: T2076810, TXGSP043, M/279825/01/1. Unpublished study prepared by Bayer Ag Inst. of Toxicology. 71 p. October 13, 2006. MRID No. 47114017
Report No &:	AT03363, T2076810
Document No:	M-279825-01-2
Guidelines:	OECD Guidelines N° 403 (12 May 1981) EEC Directive 92/69/EEC Annex V – Method B2 (1992) EPA: OPPTS 870.1300 (1998) MAFF, notification 12 Nousan-8147 (2000)
GLP	Yes

I. Materials and methods

1. Test material:	BYH 18636 (7.45%w/w) + Isoxaflutole (18.5% w/w) + AE 0001789 (12.5% w/w) SC 90 + 225 + 150 g/L
Specification no.:	102000013459
Description:	White milky liquid
Lot/Batch no.:	2006-004041
Content:	BYH 18636: 90 g/L, Isoxaflutole 225 g/L, AE 0001789: 150 g/L (Nominal values) BYH 18636: 86.2 g/L, Isoxaflutole 214 g/L, AE 0001789: 144 g/L (Certified by analysis)
Stability of test compound:	Guaranteed for study duration; expiry date: 8th May 2007
2. Vehicle and/or positive control:	The test article was aerosolised as aqueous solution.
3. Test animals	
Species:	Rat, males and females
Strain:	SPF Wistar (Hsd Cpb:WU)
Age:	Approximately two months
Weight at dosing:	Males: 186 g – 196 g Females: 179 g – 188 g
Source:	Harlan/Winkelmann GmbH, Borchen, Germany
Acclimation period:	At least 5 days

Diet:	Provimi Kliba 3883 9441 pellets, Kaiseraugst, Switzerland
Water:	tap water *ad libitum*
Housing:	During the acclimation and study periods, the animals were housed singly in conventional Makrolon® Type III cages (based on A. Spiegel and R. Gönnert, Zschr. Versuchstierkunde, 1, 38 (1961) and G. Meister, Zschr. Versuchstierkunde, 7, 144-153 (1965)). Cages were changed twice a week while unconsumed feed and water bottles were changed once per week. The legal requirements for housing experimental animals (Directive 86/609 EEC) were followed. Bedding consisted of type BK8/15 low-dust wood granulate from Ssniff, Soest/Westfalen, Germany. The wood granulate was randomly checked for harmful constituents at the request of the Laboratory Animal Services, Bayer Healthcare AG. Room temperature: 22 ± 2°C; Air humidity: 40-60%; Ventilation: approx. 10 changes per hour; Light/Dark cycle: 12 hour rhythm.

B. Study design and methods

1. Animal assignment and treatment

One group of 10 Wistar rats (5 animals/sex) was exposed to mean aerosol concentration of 2.607 mg/L for up to 4 hours using nose only exposure system. Attempts were made so that liquid aerosol generated was respirable to rats. The test item was aerosolised undiluted.

Dose:	0 – 2.607 mg/L air (maximum technically attainable concentration)
Application route:	Inhalation (nose-only exposure)
Duration:	4 hours
Group size:	5 rats/dose/sex
Post-treatment observation period:	14 days
Observations:	Mortality, clinical signs, body weights, rectal temperature, reflex measurements, gross necropsy
In life dates:	10th July 2006 to 24th July 2006

2. Generation of the test atmosphere / chamber description

Generation and characterization of chamber atmosphere

Target concentration (mg/L)	Nominal concentration (mg/L)	Mean achieved concentration (mg/L)	Mean mass Aerodynamic Diameter (µm)	Geometric standard deviation (µm)	Respirable fraction (% < 3 µm)
5.000	18.544	2.607	3.4	2.57	45

II. Results and discussion

A. Mortality

Mortality was not observed at 2.607 mg/L air.

Table 7.1.3-1 Doses, mortality / animals treated

Actual concentration (mg/L air)	Toxicological results*			Duration of signs	Time of death	Mortality [%]
Males						
0	0	0	5	--	--	0
2.607	0	0	5	--	--	0
Females						
0	0	0	5	--	--	0
2.607	0	0	5	--	--	0
acute inhalation LC_{50}: > 2.607 mg/L air						

* 1st number = number of dead animals; 2nd number = number of animals with signs; 3rd number = number of animals exposed

B. Clinical observations

All rats tolerated the exposure without specific signs.
Reflex measurements: no exposed rats exhibited changes in reflexes.
Rectal temperature: no significant changes.

C. Body weight

Body weights: no significant changes.

D. Necropsy

Effects on organs: necropsy findings were unremarkable in rats sacrificed at the end of the observation period.

III. Conclusion

The acute inhalation LC_{50} of the test substance for males and females is greater than 2.607 mg/L, which is consistent with the criteria for EPA Tox Category IV.

EVALUATION, SUMMARY AND CONCLUSION BY REGULATORY AUTHORITY	
Name of authority	Pesticides Safety Directorate, UK
Reviewer's Comments	Reliability rating: Totally reliable The study (T2073810) is fully compliant with OECD 403 (1987) The Notifier's summary states that no significant effects were observed on rectal temperature, however the mean rectal temperature of the exposed group of females (37.2°C) was statistically significantly ($p<0.05$) lower than that of control females (38.2°C). The mean rectal temperature of the exposed group of males (37.7°C) was comparable to the control males (38.2°C). Findings indicate that the test material may be a mild respiratory irritant; however, the absence of clinical signs is notable.
Conclusions	The acute inhalation LC_{50} of the test material in the rat was found to be >2.607 mg/l, stated to be the maximum concentration technically achievable under the conditions of this study. The product is therefore not classified for acute inhalation toxicity according to current EC criteria. The slight (but statistically significant) reduction in body temperature seen in treated females indicates that the product may be a mild respiratory irritant, however classification of the product as a respiratory irritant is not considered to be appropriate in the absence of any correlating clinical signs.

Reviewer: Pesticides Safety Directorate, UK **Date: August 1, 2008**
Risk Manager (EPA): RM 25

Primary eye irritation

Report:	**KIIIA1 7.1.5/01, Gmelin, C., 2006**
Title:	BYH 18636 + Isoxaflutole + AE 0001789 SC 90 + 225 + 150 g/L – Acute eye irritation in rabbits
Citation:	Gmelin, C. (2006) BYH 18636 + Isoxaflutole + (Inert Ingredient) SC 90 + 225 + 150 g/l: Acute Eye Irritation on Rabbits. Project Number: T/0076584, AT03244, M/277838/01/1. Unpublished study prepared by Bayer Ag Inst. of Toxicology. 23 p. August 9, 2006. MRID No. 47114018
Report No & Document No	AT03244, T0076584 M-277838-01-2
Guidelines:	OECD: No. 405, 24th April 2002 EEC Directive 67/548 Annex V – Method B.5 (1967) EPA OPPTS 870.2400, United States EPA 712-C-98-195 (1998)
GLP	Yes

I. Materials and methods

A. Materials

1. Test material:	BYH 18636 (7.45%w/w) + Isoxaflutole (18.5% w/w) + AE 0001789 (12.5% w/w) SC 90 + 225 + 150 g/L
Specification no.:	102000013459
Description:	White milky liquid
Lot/Batch no:	2006-004041
Content:	BYH 18636: 90 g/L, Isoxaflutole 225 g/L, AE 0001789: 150 g/L (Nominal values) BYH 18636: 86.2 g/L, Isoxaflutole 214 g/L, AE 0001789: 144 g/L L (Certified by analysis)
Stability of test compound:	Guaranteed for study duration; expiry date: 8th May 2007
2. Vehicle and/or positive control:	None
3. Test animals	
Species:	Rabbit, females
Strain:	Albino (Crl:KBL(NZW)BR)
Age:	Young adult animals
Weight at dosing:	2.7 kg – 2.9 kg
Source:	Charles River, Kißlegg, Germany
Acclimation period:	At least 5 days
Diet:	Ssniff K-Z, Soest, Germany

Water:	Tap water *ad libitum*
Housing:	The animals were housed individually in cage units Metall/Noryl by EBECO. Excrement trays below the cages contained low dust wood granulate bedding (J. Rettenmaier & Söhne, 73479 Ellwangen-Holzmühle, Germany). The wood granulate was changed at least twice weekly. The animal room had a standardized climate: Room temperature: 20 ± 3°C; Air humidity: 50 ± 25%; Light/Dark cycle: 12 hour rhythm.

B. Study design and methods

1. Animal assignment and treatment

A single dose of 0.1 mL of the undiluted test item was instilled under the lower lid of the left eye of one rabbit. The right eye was untreated and served as the control. The eyes were not rinsed after administration of the test item. Since the test item was not severely irritant on the first animal, it was then evaluated in two other animals. Ocular reactions were observed approximately 1 hours, 24, 48 and 72 hours after instillation and then daily until the end of the observation period.

Dose:	0.1 mL pure liquid test substance/animal
Application route:	Instillation into the conjunctival sac of one eye. The eye was not rinsed for at least 24 hours following instillation.
Group size:	3 rabbits
Observations:	Clinical signs, eye effects, body weight (at beginning of study)
In life dates:	4th July 2006 to 7th July 2006

II. Results and discussion

A. Findings

Under the present test conditions the following findings were noted:

The individual findings of the treated eyes at the various observation times are summarized in the table below. The control eyes did not show any abnormal findings and are not listed in the Table 7.1.5-1. One hour after application, the test compound adhered to conjunctivae of animals 1 and 3.

Table 7.1.5-1 Summary of Irritant Effects (Scores)

Animal No Sex	Parameter	1h	24h	48h	72h	Index* 24-48-72h	Reversible (days)
1 F	Chemosis	0	0	0	0	0.0 (-)	NA
	Conjunctival redness	2	1	0	0	0.3 (-)	2
	Iris lesions	0	0	0	0	0.0 (-)	NA
	Corneal opacity	0	0	0	0	0.0 (-)	NA
2 F	Chemosis	0	0	0	0	0.0 (-)	NA
	Conjunctival redness	2	2	0	0	0.7 (-)	2
	Iris lesions	0	0	0	0	0.0 (-)	NA
	Corneal opacity	0	0	0	0	0.0 (-)	NA
3 F	Chemosis	1	0	0	0	0.0 (-)	NA
	Conjunctival redness	2	1	0	0	0.3 (-)	2
	Iris lesions	0	0	0	0	0.0 (-)	NA
	Corneal opacity	0	0	0	0	0.0 (-)	NA

* = Mean of scores on 24-48-72h instillation

Response: corneal opacity: mean scores <2 = (-), ≥2<3 = (+), ≥3 = (++)
Iritis: mean scores <1 = (-), ≥1<2 = (+), =2 = (++)
Conjunctival redness: mean scores <2.5 = (-), ≥2.5 = +
Conjunctival oedema: mean scores <2 = (-), ≥ 2 = +
NA = not applicable

III. Conclusion

According to OECD classification criteria, BYH 18636 + Isoxaflutole + AE 0001789 SC 90 + 225 +150 g/L is not irritating to eyes. Based on the EPA guidelines, the formulation is in EPA Tox Category III.

EVALUATION, SUMMARY AND CONCLUSION BY REGULATORY AUTHORITY	
Name of authority	Pesticides Safety Directorate, UK
Reviewer's comments	Reliability rating: Totally reliable The study (T0076584) is fully compliant with OECD 405 (2002)
Conclusions	The test material was found to be a slight eye irritant under the conditions of this study and is not classified as an eye irritant according to current EC criteria.

Reviewer: Pesticides Safety Directorate, UK **Date: August 1, 2008**
Risk Manager (EPA): RM 25

Primary dermal irritation

Report:	**KIIIA1 7.1.4/01, Gmelin, C.; 2006**
Title:	BYH 18636 + Isoxaflutole + AE 0001789 SC 90 + 225 + 150 g/L – Acute skin irritation/corrosion on rabbits
Citation:	Gmelin, C. (2006) BYH 18636 + Isoxaflutole +(Inert Ingredient) SC + 90 + 225 +150 g/l: Acute Skin Irritation/Corrosion on Rabbits. Project Number: T/9076583, AT03245, M/278731/01/1. Unpublished study prepared by Bayer Ag Inst. of Toxicology. 23 p. August 9, 2006. MRID No. 47114019
Report No & Document No	AT03245, T9076583 M-278731-01-2
Guidelines:	OECD: No. 404, 24th April 2002 EEC Directive 67/548 Annex V – Method B.4 (1967) in its current version EPA OPPTS 870.2500 United States EPA 712-C-98-196 (1998)
GLP	Yes

I. Materials and methods

A. Materials

1. Test material: BYH 18636 (7.45%w/w) + Isoxaflutole (18.5% w/w) + AE 0001789 (12.5% w/w) SC 90 + 225 + 150 g/L

Article no.:	102000013459
Description:	White milky liquid
Lot/Batch no:	2006-004041
Content:	BYH 18636: 90 g/L, Isoxaflutole 225 g/L, AE 0001789: 150 g/L (Nominal values) BYH 18636: 86.2 g/L, Isoxaflutole 214 g/L, AE 0001789: 144 g/L (Certified by analysis)
Stability of test compound:	Guaranteed for study duration; expiry date: 8th May 2007

2. Vehicle and/or positive control: None

3. Test animals

Species:	Rabbit, females
Strain:	Albino (Crl:KBL(NZW)BR)
Age:	Young adult animals
Weight at dosing:	2.7 kg – 3.1 kg
Source:	Charles River, Kißlegg, Germany
Acclimation period:	At least 5 days

Diet:	Ssniff K-Z, Soest, Germany
Water:	Tap water *ad libitum*
Housing:	The animals were housed individually in cage units Metall/Noryl by EBECO. Excrement trays below the cages contained low dust wood granulate bedding (J. Rettenmaier & Söhne, 73479 Ellwangen-Holzmühle, Germany). The wood granulate was changed at least twice weekly. The animals were regularly transferred to clean cages. The animal room had a standardized climate: Room temperature: 20 ± 3°C; Air humidity: 50 ± 25%; Light/ Dark cycle: 12 hour rhythm.

B. Study design and methods

1. Animal assignment and treatment

Doses of 0.5 mL of the undiluted test item were applied to the clipped, intact skin of three rabbits under a gauze patch for 4 hours. The treatment site was observed shortly after the end of the exposure period then daily for up to 72h.

Dose:	0.5 mL pure liquid test substance/animal
Application route:	Dermal (semi occlusive procedure)
Duration:	4 hours
Group size:	3 rabbits
Observations:	Clinical signs, skin effects, body weight (at beginning of study)
In life dates:	27th June 2006 to 30th June 2006

II. Results and discussion

A. Findings

Under the present test conditions the following findings were noted.
There were no systemic intolerance reactions.

Table 7.1.4-1 Summary of irritant effects (Scores)

Rabbit number and sex	E or O	Scores Time after application						Mean score 24-48-72h	Response	Reversibility (days)
		1h	24h	48h	72h	D7	D14			
1 F	E	0	0	0	0	-	-	0.0	(-)	NA
	0	0	0	0	0	-	-	0.0	(-)	NA
2 F	E	0	0	0	0	-	-	0.0	(-)	NA
	0	0	0	0	0	-	-	0.0	(-)	NA
3 F	E	0	0	0	0	-	-	0.0	(-)	**NA**
	0	0	0	0	0	-	-	0.0	(-)	**NA**

E = erythema, O = oedema
No positive response (-): mean score 24-48-72h < 2 Positive response (+): mean score 24-48-72h ≥ 2
NA = not applicable, - examination not performed
*: in respect of the result 1h post application

III. Conclusion

According to classification criteria, BYH 18636 + Isoxaflutole + AE 0001789 SC 90 + 225 + 150 g/L is not a dermal irritant, which is consistent with the criteria for EPA Tox Category IV.

EVALUATION, SUMMARY AND CONCLUSION BY REGULATORY AUTHORITY	
Name of authority	Pesticides Safety Directorate, UK
Reviewer's comments	Reliability rating: Totally reliable The study (T9076583) is fully compliant with OECD 404 (2002)
Conclusions	The test material was found to be non-irritating to skin under the conditions of this study. The product is therefore not classified according to current EC criteria.

Reviewer: Pesticides Safety Directorate, UK **Date: August 1, 2008**
Risk Manager (EPA): RM 25

Skin sensitization

Report:	**KIIIA1 7.1.6/01 Repetto-Larsay, M., 2006**
Title:	BYH 18636 + IFT + AE 0001789 SC 90 + 225 + 150 g/L - Evaluation of potential dermal sensitization in the local lymph node assay in the mouse.
Citation:	Repetto-Larsay, M. (2006) BYH 18636 + IFT + (Inert Ingredient) SC 90 + 225 + 150 g/l: Evaluation of Potential Dermal Sensitization in the Local Lymph Node Assay in the Mouse. Project Number: SA/06027, M/271415/01/1. Unpublished study prepared by Bayer Cropscience. 41 p. May 16, 2006. MRID No. 47114020
Report No.:	SA 06027
Doc. No.:	M-271415-01-2
Guidelines:	O.E.C.D. Guideline 429 (2002)
GLP	Yes

I. Materials and methods

A. Materials

1. Test material:	BYH 18636 (7.26% w/w) + Isoxaflutole (18.3% w/w) + AE 0001789 (12.1%) SC 90 + 225 + 150 g/L
Specification no.:	102000013459
Description:	White milky liquid
Lot/Batch no:	2005-004304
Content:	BYH 18636: 90 g/L, Isoxaflutole 225 g/L, AE 0001789: 150 g/L (Nominal values) BYH 18636: 85.2 g/L, Isoxaflutole 215 g/L, AE 0001789: 142 g/L L (Certified by analysis)
Stability of test compound:	Guaranteed for study duration; expiry date: 16th Dec 2006

2. Vehicle and/or positive control:	Vehicle: Water containing 1% Pluronic Acid was selected to ensure compatibility with the test substance and maximum wetting of the mouse ears with the maximum possibility of skin penetration of the various formulation ingredients. A positive control group received 0.25% p-benzoquinone in 25% BYH 18636 + Isoxaflutole + AE 0001789 SC 465 and 75% Pluronic acid at 1% in water. The positive control was spiked in the formulation to ensure that under the conditions of this assay, the study demonstrated appropriate sensitivity with the positive control.

3. Test animals

Species:	Mice, females
Strain:	CBA/J
Age:	At least 8 weeks old
Source:	R. Janvier, le Genest St Isle, France
Acclimation period:	At least 5 days
Diet:	Certified rodent pellet diet: AO4C-10, S.A.F.E. (Scientific Animal Food and Engineering, Route de Saint Bris, Augy, France)
Water:	Tap water *ad libitum*
Housing:	During the study period the animals were individually housed in suspended, stainless steel, wire mesh cages. Room temperature: 20-24°C Humidity: 40 - 70 %; Light/dark cycle: Twelve hours rhythm Air exchange rate: 10-15 times per hour.

B. Study design and methods

Animal assignment and treatment

Twenty-four female CBA/J mice were allocated to 6 groups of four animals each and these were treated as outlined below:
Four groups received the test substance at a concentration of 10, 25, 50 or 100% in vehicle (aqueous pluronic acid at 1%);
A positive control group received 0.25% p-benzoquinone in 50% BYH 18636 + IFT + AE 0001789 SC 90 + 225 + 150 g/L and 50% Pluronic acid at 1% in water. The positive control was spiked in the formulation to ensure that under the conditions of this assay, the study demonstrated appropriate sensitivity with the positive control;
A control group received the vehicle, 1% pluronic acid in water.

Observations:	Mortality, clinical signs, skin effects, body weight (at beginning and termination of study)
In life dates:	24th March 2006 to 5th April 2006

The test substance, positive control or the vehicle were applied on external surfaces of each ear (25 µL/animal) for three consecutive days (Days 0, 1 and 2) at the appropriate concentrations. On Day 5, the cell proliferation in the local lymph nodes was measured by incorporation of tritiated thymidine and the obtained values were used to calculate proliferation indices.

II. Results and discussion

A. Findings

Mortality and clinical signs - No mortality and no clinical signs were observed during the study. No cutaneous reactions were observed at the treated site for the negative control, positive control or BYH 18636 + IFT + AE 0001789 SC 90 + 225 + 150 g/L treated groups.

Body weights - No significant body weight changes were observed during the study either in the control or in the treated groups.

The proliferation index values of the test substance were 1.6, 1.2, 1.5 and 2.3 at treatment concentrations of 10, 25, 50 and 100% respectively.

The proliferation index value of the positive control was 14.8 at treatment concentration of 0.25% of p-Benzoquinone

GROUP	TEST SUBSTANCE(S)	# OF ANIMALS	CONCENTRATION % DAYS 0-2	DPM/NODE	STIMULATION INDEX (SI)
1	Vehicle control	4	0	394	
2	BYH 18636 + Isoxaflutole AE 0001789 SC 465	4	10	614	1.6
3		4	25	482	1.2
4		4	50	607	1.5
5		4	100	924	2.3
6	p-Benzoquinone	4	0.25	5826	14.8

* DPM = disintegrations per minute
** SI = DPM of treated group / DPM of control group

III. Conclusion

No stimulation index value was over 3 for the treated groups and as no dose-related effect was noticed, BYH 18636 + IFT + AE 0001789 SC 90 + 225 + 150 g/L was found to be not a sensitizing formulation in the Local Lymph Node Assay.

The 2003 OPPTS harmonized guidelines state the "LLNA is the preferred method, where applicable." The "where applicable" correlates to the performance parameters in the appendix — the 1999 ICCVAM report. In 1999, ICCVAM validated the method using 209 "single compound compounds" but did not validate the assay for mixtures. The appendix clearly states the LLNA should not be used for metals, aqueous solutions, and mixtures. In January 2008, ICCVAM updated the validation report on LLNA regarding mixtures, metals and aqueous solutions. ICCVAM findings are that when compared to the guinea pig it has a false negative rate of 50%, a false positive rate of 44%, and accuracy rate of 53% in mixtures. Due to these limitations, EPA questioned whether the negative result found in this study is correct. EPA decided to perform a weight of the evidence approach for this joint review chemical by obtaining information on each component (inerts ingredient) in this mixture. After reviewing the components sensitization potential, EPA determined that most were non-sensitizers and other components were assumed to be below the sensitizing threshold. Therefore, to avoid further animal testing EPA will classify the study as "supplemental" and recommend label language as a non-sensitizer for SC 465[BYH 18636 + AE 0001789 + IFT SC 465].

EVALUATION, SUMMARY AND CONCLUSION BY REGULATORY AUTHORITY	
Name of authority	Pesticides Safety Directorate, UK
Reviewer's comments	Reliability rating: Totally reliable The study (SA 06027) is fully compliant with OECD 429 (2002) Some evidence of weak sensitisation (stimulation index of 2.3) was seen at the highest concentration (100%) of the test material, however a concentration response is not apparent and the stimulation index is not sufficiently high (stimulation index of ≥3). The response to the positive control compound is slightly high, but is not considered to be excessive and therefore meets the requirements of the guideline.
Conclusions	Evidence of weak sensitisation was seen under the conditions of this study, however the findings are not of sufficient magnitude to trigger classification according to current EC criteria.

SUMMARY OF ACUTE TOXICTY STUDIES BY REGULATORY AUTHORITY
Name of authority: Pesticides Safety Directorate, UK The product 'BYH 18636 + Isoxaflutole AE 0001789 SC 90 + 225 + 150' ('SC465') was found to be of low toxicity to the rat by the oral, dermal and inhalation routes. No treatment-related findings were observed in the acute oral toxicity study at a limit dose of 2000 mg/kg bw. Findings in the acute dermal toxicity study were limited to a minimal effect on bodyweight at the limit dose level of 2000 mg/kg bw. A slightly (but statistically significantly) lower body temperature was seen in the acute inhalation toxicity study at the maximum achievable concentration of 2.607 mg/l. The effect on body temperature in this study is consistent with a mild respiratory irritant effect, however no correlating clinical signs were observed. The product was found to be non-irritant to skin irritant and a slight eye irritant. Some evidence of weak skin sensitisation was seen in a Local Lymph Node Assay (SI =2.3 at the highest concentration of 100%), however the magnitude of response is not sufficient to trigger classification of the product as a skin sensitiser. The product is not classified for acute toxicity, irritation or sensitisation based on the results of these studies (Table 7.1). MSDSs for the co-formulants do not raise any additional concerns of relevance to classification at the levels proposed.

Table 7-1 Summary of acute toxicity studies

According to the US and Canadian classification criteria, the formulation is labelled as follows:

Guideline No.	Study Type	Results	Toxicity Category
81-1	Acute Oral	LD_{50} = > 2000 mg/kg in males & females	III
81-2	Acute Dermal	LD_{50} = >2000 mg/kg in males &, females	III
81-3	Acute Inhalation (4 h)	LC_{50} = >2.607 mg/L in males & females	IV
81-4	Primary Eye Irritation	Moderate redness of the conjunctivae, reversed within 48 hrs	III
81-5	Primary Skin Irritation	not a dermal irritant	IV
81-6	Dermal Sensitization	not a dermal sensitizer	N/A

1. **DP BARCODE:** D340543
2. **PC CODES:** 015804, 123000
3. **CURRENT DATE:** August 1, 2008
4. **TEST MATERIAL:** [a]BYH 18636 + Isoxaflutole +AE 0001789 SC 90 +225 +150 g/L (7.26% w/w BYH 18636, 18.3% w/w AE B197278 (isoxaflutole) and 12.1% AE 0001789; density 1.174 g/mL; Batch No. 2005-004304; pH 3.8; white milky liquid)

[b]BYH 18636 + Isoxaflutole +AE 0001789 SC 90 +225 +150 g/L (7.45% w/w BYH 18636, 18.5% w/w AE B197278 (isoxaflutole) and 12.5% AE 0001789; density 1.157 g/mL; Batch No. 2006-004041; pH 3.9; white milky liquid)

Study/Species/Lab Study # /Date	MRID	Results	Tox. Cat.	Core Grade
[a]Acute oral toxicity / rat Bayer HealthCare AG AT03049, T 7076608 May 23, 2006	47114015	LD_{50} > 2000 mg/kg (males and females)	III	A
[a]Acute dermal toxicity / rat Bayer HealthCare AG AT03067, T 8076609 May 24, 2006	47114016	LD_{50} > 2000 mg/kg (males and females)	III	A
[b]Acute inhalation toxicity/ rat Bayer HealthCare AG AT03363, T 2076810 October 13, 2006	47114017	LC_{50} > 2.607 mg/L (males and females)	IV	A
[b]Primary eye irritation / rabbit Bayer HealthCare AG AT03344, T 0076584 August 9, 2006	47114018	Conjunctival redness at 1 hour in 3/3 eyes resolving by 48 hours	III	A
[b]Primary dermal irritation / rabbit Bayer HealthCare AG AT03245, T 9076583 August 9, 2006	47114019	No irritation observed	IV	A
[a]Dermal sensitization / mouse Bayer CropScience SA 06027 May 16, 2006	47114020	Not a sensitizer	-	S

Core Grade Key: A = Acceptable, S = Supplementary, U = Unacceptable, W = Waived